REMARKS

Claims 1, 4, 6, 10-16, and 39-46 were under examination as of the issuance of the Final Office Action. In the Amendment to the Claims spanning pages 2 to 4 of this paper, claims 6, 10, 41, 45 and 46 have been amended and new claims 47 and 48 have been added. Accordingly, upon entry of the amendments presented herein, claims 1, 4, 6, 10-16 and 39-48 will remain pending.

Support for the foregoing claim amendments and the new claims may be found throughout the specification and originally filed claims. Specifically, support for the amendments to claims 6, 41, 45 and 46 can be found at, for example, page 24, line 31 to page 25, line 5 of the specification. Support for new claims 47 and 48 can be found at, for example, page 29, lines 4-18 of the specification.

No new matter has been added by these claim amendments or the introduction of the new claims. Any amendments to the claims have been made solely in the interest of expediting examination and in no way acquiescing to the validity of the Examiner's rejections. Applicants reserve the right to pursue the claims as originally filed in one or more further applications.

Information Disclosure Statement

The Examiner has indicated that references D1 and D2 cited in the PTO Form SB-08, submitted on July 28, 2005, were not considered. Pursuant to a telephonic conversation with Examiner Hutson on April 11, 2006, Applicants re-submit herewith a copy of the PTO Form SB-08 filed on July 28, 2005 citing references D1 and D2. Applicants respectfully request that the Examiner initial the PTO Form SB-08 and return a copy of the initialed form to Applicants to signify that references D1 and D2 cited therein have been considered and made of record in the present application.

Acknowledgement of the Examiner's Withdrawal of the Objection to the Specification

The Examiner has withdrawn the previous objection to the specification. However, the Examiner states that the rejection was withdrawn

> because it is recognized that sequences at least 60% homologous to each other do typically remain hybridized to each other when hybridization conditions are

> under stringent conditions, and when those sequences are at least 90% or 95% homologous to each other. As sequences which are at least 90% or 95% homologous to each other, are at least 60% homologous to each other, the objection is withdrawn.

Applicants gratefully acknowledge the Examiner's withdrawal of the previous objection to the specification and respectfully submit that one skilled in the art would appreciate that sequences of even 60% homology to each other are capable of hybridizing to each other under stringent hybridization conditions, as evidenced, for example, by U.S. Patent No. 6,436,684.

Rejection of Claims 6, 10-16 and 41-46 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 6, 10-16 and 41-46 under 35 U.S.C. § 112, first paragraph as not being sufficiently enabled. In particular, the Examiner is of the opinion that the specification

> does not reasonably provide enablement for any isolated nucleic acid molecule [comprising] a nucleotide sequence which is a mere 90% identical to the nucleotide sequence of SEQ ID NO: 1, wherein said nucleic acid molecule encodes a polypeptide which is capable of functioning as an extracellular nuclease, and vectors and host cells comprising said nucleic acid... [A]pplicants are reminded that the current rejection is based on a lack of enablement, not a lack of written description. Second while examples in the *Revised Interim Written Description Guidelines Training Materials* are helpful for using to determine if a claimed genus is adequately described, they are only guidelines, and in addition to any guidelines for written description or enablement, a number of other application specific variables must be considered in order to determine whether a claimed genus is adequately described and sufficiently enabled...

Applicants traverse the foregoing rejection for the following reasons. Once again, Applicants direct the Examiner's attention to Example 14 of the Written Description Guidelines, which states that claims directed to sequences of 95% identity to a disclosed sequence and characterized by a particular function are sufficiently enabled in accordance with 35 U.S.C. § 112, first paragraph, where the specification discloses an assay for identifying such sequences. Indeed, the present specification provides extensive guidance for making and identifying such sequences, for example, in Examples 4-9 at page 51, line 32 to page 57, line 27 of the specification and in Example 11 at page 58, line 28 to page 60, line 10 of the specification. Specifically, at page 51, line 32 to page 53, line 18, Applicants teach methods for the *in vivo*

mutagenesis of bacterial strains and methods of transferring mutated nucleic acid molecules (*e.g.*, of 95% identity to the nucleotide sequence of SEQ ID NO:1) into such bacterial strains. In addition, at page 53, line 20 to page 54, line 6, Applicants teach assays for assessing the expression of the mutated protein in the bacterial strains. At page 56, lines 4-31, Applicants teach assays for assessing the function and activity of the mutated protein (*e.g.*, to determine whether the mutated protein retains extracellular nuclease activity). Furthermore, at page 56, line 33 to page 57, line 27, Applicants teach methods for determining the effect of the mutated protein on the production of the desired product, for example, methionine, from cultured bacteria. Additionally, at page 58, line 28 to page 60, line 10, Applicants teach techniques for identifying sequence identity, for example, for identifying sequences of at least 95% or 97% identity to SEQ ID NO:1. Clearly, the specification provides extensive teachings to enable one skilled in the art to design and assess the activity of sequences of 95% or 97% identity to those of SEQ ID NO:1.

Moreover, Applicants submit that, even though Example 14 is part of the *Written Description Guidelines* and not the *Enablement Guidelines*, this example does state explicitly that ***one skilled in the art would be able to generate a nucleotide sequence of 95% identity to another nucleotide sequence using only routine experimentation***. Specifically, the relevant section of Example 14 provides that "*[t]he procedures for making variants of SEQ ID NO:3* ***are conventional in the art*** *and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are* ***conventional in the art***" **(Emphasis added)**.

Accordingly, while the *Written Description Guidelines* are generally directed to describing the standard for satisfying the written description requirement, in this particular example, the Guidelines clearly provide guidance on the USPTO's position regarding a key question for determining whether the enablement requirement has been satisfied: would it be routine for one of skill in the art to generate a sequence with 95% identity to a specified nucleotide or amino acid sequence and which retains the activity of the specified nucleotide or amino acid sequence? The answer to that question, as provided by the USPTO, is: yes. The Guidelines provide that claims to sequences of 95% identity with a functional limitation are sufficiently enabled where

the specification provides assays for the identification of such sequences having the requisite function. Accordingly, because it is conventional, *i.e.*, routine, to make nucleotide or amino acid sequences of at least 95% identity to a specified nucleotide or polypeptide molecule and because the instant specification provides assays for identifying such sequences having the desired activity (as detailed above), one of skill in the art would be able to make and use the claimed invention using only routine experimentation.

The Examiner is further of the opinion that

> the specification does not establish: (A) regions of the protein structure which may be modified without effecting "extracellular nuclease" activity; (B) the general tolerance of "extracellular nuclease" to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of an "extracellular nuclease" with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the "extracellular nuclease" activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable..., it would require undue experimentation for one skilled in the art to arrive at the majority of those nucleic acid molecules of the claimed genus encoding polypeptides with the claimed "extracellular nuclease" activity.

Applicants respectfully submit that, in view of the teachings in the present application and the general knowledge in the art at the time of the filing of the present application, it would have been well within the ability of a skilled artisan to make and use sequences of at least 95% identity to the nucleotide and amino acid sequences of SEQ ID NOs:1 and 2, respectively. Indeed, the identification and manipulation of certain residues, without affecting protein function, would have been well within the ability of one skilled in the art. To begin with, Applicants submit that conserved domains among nucleases were determinable by comparison of the claimed sequences to homologous sequences known in the art at the time of the filing of the present invention. For example, Applicants direct the Examiner's attention to GenBank Accession Nos. AAB39273 (published December 24, 1996) and AAF12592 (published November 16, 1999), submitted herewith as Appendices A and B, respectively, both of which disclose the nucleic acid and corresponding amino acid sequences of extracellular nucleases. Accordingly, upon comparison and

identification of conserved domains among SEQ ID NO:2 and these aforementioned sequences, one of skill in the art would be able to determine those nucleotide and amino acid residues which could be manipulated without affecting protein function.

Moreover, Applicants submit that the specification teaches the manipulation of sequences of the invention (for example, SEQ ID NOs:1 and 2) without affecting the function of the sequences. Specifically, the specification teaches random mutagenesis techniques such as saturation mutagenesis (for example, as described at page 51, line 32 to page 53, line 18 and page 28, line 28 to page 30, line 19 of the specification) and subsequent assays for identifying the function of the mutagenized protein (for example, as described at page 56, lines 4-31 of the specification) to identify mutagenized sequences which retain extracellular nuclease activity. Specifically, the specification states

> one of ordinary skill in the art will further appreciate that changes can be introduced by mutation into a nucleotide sequence of Appendix A, thereby leading to changes in the amino acid sequence of the encoded RRP protein, without altering the functional ability of the RRP protein. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in a sequence of Appendix A... mutations can be introduced randomly along all or part of an RRP coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for an RRP activity described herein to identify mutants that retain RRP activity. Following mutagenesis of one of the sequences of Appendix A, the encoded protein can be expressed recombinantly and the activity of the protein can be determined using, for example, assays described herein (see Example 8 of the Exemplification). (see page 28, line 29 to page 30, line 19 of the specification).

Accordingly, because the specification teaches techniques for random mutagenesis of sequences without affecting function and corresponding assays for determining the activity of the mutagenized sequences, and, further, because conserved domains could be determined, for example, by comparison to sequences known in the art at the time of the filing of the present application, one of skill in the art would be able to make and use the claimed invention using only routine experimentation.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 6, 41, 45, 46, and claims depending therefrom, under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants believe that the foregoing amendments and remarks render the application in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

The Commissioner is hereby authorized to charge any deficiency in the fees paid herewith, or credit any overpayment, to Deposit Account No. 12-0080, under Order No. BGI-130CP, from which the undersigned is authorized to withdraw.

Dated: April 18, 2006

Respectfully submitted,

By _____

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Attorney for Applicants
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109

1: AAB39273. Reports nuclease...[gi:1185049]

Features Sequence

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REFERENCE   1  (residues 1 to 1070)
  AUTHORS   Dodd,H.N. and Pemberton,J.M.
  TITLE     Cloning, sequencing, and characterization of the nucH gene encoding
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  JOURNAL   J. Bacteriol. 178 (13), 3926-3933 (1996)
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1: AAF12592. Reports extracellular nuc...[gi:6460888]

BLink, Conserved Domains, Links

Features Sequence

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            Dodson,R.J., Haft,D.H., Gwinn,M.L., Nelson,W.C., Richardson,D.L.,
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  TITLE     Genome sequence of the radioresistant bacterium Deinococcus
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  JOURNAL   Science 286 (5444), 1571-1577 (1999)
  MEDLINE   20036896
REFERENCE   2  (residues 1 to 1067)
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            Dodson,R.J., Haft,D.H., Gwinn,M.L., Nelson,W.C., Richardson,D.L.,
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            Smith,H.O., Venter,J.C. and Fraser,C.M.
  TITLE     Direct Submission
  JOURNAL   Submitted (02-NOV-1999) The Institute for Genomic Research, 9712
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